Effect of distance to specialist care for the diagnosis and disease outcome of inflammatory bowel disease in the Swiss inflammatory bowel disease cohort study

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Abstract: Background: Inflammatory bowel disease (IBD) needs early interventions and an individual specialist-patient relationship. Distance from a tertiary IBD center might affect patient's disease course and outcome. We investigated whether the patient-to-specialist distance has an impact on the disease course using the well-defined patient collective of the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). Methods: Patient's home address at diagnosis (postal zip code) was extracted from the SIBDCS database. Distance between each zip code and the nearest located IBD specialist center was calculated and classified into the following three sections based on proximity: <10 km (group 1); 10-35 km (group 2); >35 km (group 3). Results: Our study included in total 408 IBD patients [234 Crohn's disease (CD), 154 ulcerative colitis (UC), 20 IBD unclassified (IBDU)]. Median age was lowest in group 2 at diagnosis (G1: 28 years; G2: 21 years, G3: 26 years, $p < 0.01$). The diagnostic delay did not differ between groups. CD patients in group 1 were treated more often with anti-tumor necrosis factor (TNF) agents (72% versus 56%, $p = 0.04$) and 5-aminosalicylates (44% versus 28%, $p = 0.04$) than in group 3. UC/IBDU patients in group 1 were treated more often with corticosteroids than patients in group 3 (83% versus 58%, $p < 0.01$). The occurrence of IBD-related surgeries did not differ between groups. Conclusions: Patient-to-specialist distance might affect drug treatment. However, disease course and the need for IBD-related surgery does not seem to be associated with a longer distance to specialist care in Switzerland.

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Effect of Distance to Specialist Care for the Diagnosis and Disease Outcome of Inflammatory Bowel Disease in the Swiss Inflammatory Bowel Disease Cohort Study

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Short title: IBD and distance to specialist

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Summary

We hypothesized, that an increase in distance between patient's home and IBD specialist might have an adverse impact on diagnosis and disease outcome. While we detected a difference in treatment, disease complications did not differ.

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Abbreviations

5ASA	5-Aminosalicylate
CD	Crohn's disease
EIM	extraintestinal manifestations
IBD	Inflammatory Bowel Disease
IBDU	IBD unclassified
PTSD	patient-to-specialist-distance
SIBDCS	Swiss Inflammatory Bowel Disease Cohort Study
UC	Ulcerative colitis

Abstract

Background: Inflammatory bowel disease (IBD) needs early and individual specialist-patient relationship. Distance from a tertiary IBD center might affect patient's disease course and outcome. We investigated whether the patient-to-specialist-distance has an impact on the disease course using the well-defined patient collective of the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS).

Methods: Patient's home address at diagnosis (postal zip code) was extracted from the SIBDCS database. Distance between every zip code and the nearest located IBD specialist center was calculated and classified into the following three sections based on proximity: <10 km (group 1); 10-35 km (group 2); >35 km (group 3).

Results: Our study included in total 408 IBD patients [(234 Crohn's disease (CD), 154 ulcerative colitis (UC), 20 IBD unclassified (IBDU)]. Median age was lowest in group 2 at diagnosis (G1: 28y; G2: 21y, G3: 26y, P<0.01). The diagnostic delay did not differ between groups. CD patients in group 1 were treated more often with anti-TNF agents (72% vs. 56%, P=0.04) and 5-aminosalicylates (44% vs. 28%, P=0.04) than in group 3. UC/IBDU patients in group 1 were treated more often with corticosteroids than patients in group 3 (83% vs. 58%, P<0.01). The occurrence of IBD-related surgeries did not differ between groups.

Conclusions: Patient-to-specialist-distance might affect the drug treatment. However, the disease course and need for IBD-related surgery does not seem to be associated with a longer distance to specialist care in Switzerland.

Key words: disease outcome; diagnostic delay; tertiary care

Introduction

The incidence of inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is increasing worldwide in adults as well as in pediatric patients [1-3]. Patients are exposed to a tremendous social and personal burden [4], due to an often chronic-relapsing disease course and associated complications, such as fistulas, abscesses or stenoses [5-7]. To shorten the delay between symptom onset and diagnosis (referred to as "diagnostic delay") is key to avoid long-term complications, hospitalizations and surgery [8]. In addition, an optimized therapy through tight and individual physician-patient relationship is necessary. Due to an increasing number of therapeutic options [9, 10], a personalized therapeutic approach often requires specialist knowledge from tertiary care centers. Barriers like the distance to such a specialist may prevent an effective access to personalized IBD care.

The travel distance to tertiary care centers is relevant for health and disease outcome [11]. Especially in oncologic diseases, increasing travel requirements result in worse disease outcome and inappropriate treatment strategies [12]. In IBD, the distance between the patient's home and specialists could therefore influence the risk of delayed diagnosis and the rate of clinical complications by hindering a close and specialized therapy monitoring. A recent study from the U.S. showed an increased need for surgery in IBD patients living at longer distances to an IBD center [13], but did not analyze, if the distance has an impact on the diagnostic delay.

We aimed to investigate, whether the distance of the IBD patient to the closest IBD specialist tertiary care center (patient-to-specialist-distance; PTSD) is associated with diagnostic delay and disease outcome parameters in a Swiss IBD patient population. We hypothesized, that an increase in distance might have an adverse impact on diagnostic delay, treatment and disease related complications.

Patients and methods

Study Population

Our data was retrieved from the database of the SIBDCS that collects data of patients with CD, UC and IBD unclassified (IBDU) all over Switzerland since November 2006. Upon consent, pediatric and adult IBD patients are enrolled by their gastroenterologists, either in hospitals or in private practices, by using specific questionnaires for enrollment and for a yearly follow-up, thus providing epidemiological, clinical and psychosocial data as well as information about health resource consumption [14]. In our study, both pediatric and adult patients were included. Tertiary care centers, basically being equivalent to university hospitals, were considered "specialized centers" (*Figure 1*). When calculating the PTSD, we used the home address at time of diagnosis as reference. Enrollment into the cohort not only occurred at time of diagnosis, but also at later time points – depending on when the treating physician enrolled the patient. To avoid unpredictable effects on PTSD and study results from patients moving to another area between the diagnosis of IBD and enrollment into the cohort, we therefore excluded all SIBDCS patients with enrollment into the cohort later than 6 months after diagnosis. Thus, moving habits after time of diagnosis were not considered in this study.

Patient parameters

IBD patients were grouped into CD and UC plus IBDU patients. The following parameters of the study cohort were recorded for analysis: demographic data (such as gender, age at diagnosis, smoking status), type of IBD, time between IBD diagnosis and last medical visit (disease duration), time between onset of symptoms as stated by the patient and diagnosis of IBD (diagnostic delay), disease phenotype, complications (fistulas, stenosis, abscess formation and colectomy), extraintestinal

manifestations (EIM) and therapeutic history as recorded in physician reports from the database. Disease phenotype was assessed at initial colonoscopy according to the Montreal classification [15] in CD [location (L1: Ileal, L2: colonic, L3: ilieocolonic, L4: isolated upper disease), behavior (B1: non-stricturing and non-penetrating, B2: stricturing, B3: penetrating, p: accompanied with perianal disease)] and in UC [location E1: Ulcerative proctitis, E2: Left sided UC, E3: Extensive UC (pancolitis)]. As "follow-up" we analyzed data from the last medical visit available in the SIBDCS data base.

Calculation of distance from home to tertiary center

Distance between every home zip code (at diagnosis) and nearest located IBD specialist center (PTSD) was calculated using the distance calculator of Google maps (https://www.google.com/maps). As measurement for the distance we used the airline. This was done to equalize data for all patients, i.e., to account for the uncertainty about how patients were travelling (e.g., by car, public transport or other means) – as this is not recorded in the SIBDCS data base. Swiss tertiary centers with specialized knowledge in IBD treatment were the following hospitals *(Figure 1)*: University Hospital Zurich, University Hospital Basel, University Hospital Bern (Inselspital), Central University Hospital Lausanne (Centre Hospitalier Universitaire Vaudois), University Hospital Geneva, Cantonal Hospital St. Gallen. Based on proximity, the cohort was divided into three groups: <10 km (group 1); 10-35 km (group 2); >35 km, (group 3). Thresholds were chosen based on Swiss topography. Group 1 should represent an urban area, group 2 should represent a suburbian/peripheral area and group 3 should represent a rural area.

Data analysis

As the strongest surrogate for adverse disease outcome, need for surgery due to IBD (treatment of fistulas, stenosis, abscess formation and bowel resections of all extents) as retrieved from surgery reports into the SIBDCS database served as primary endpoint, whereas diagnostic delay, need for therapy with biologicals (anti-TNF agents (infliximab, adalimumab, certolizumab, golimumab) and vedolizumab (other biologics)) or immunomodulators (azathioprine, 6-mercaptopurin, methotrexate) were defined as secondary endpoints. In addition, demographic data were compared between distance groups. All statistical analyses were done using Stata software (version 14.2, StataCorp, College Station, TX, USA). Categorical data were summarized as raw frequencies and relative percentages. Differences in categorical data distributions between independent groups were assessed using the Chi-square test, or the Fisher's exact test in case of low sample size. Continuous data distribution was assessed using normal QQ-plots; normally distributed data was summarized as mean and standard deviation (SD); non-normally distributed data was summarized as median and interquartile range (IQR). Differences between means were assessed using Student's t-test, or ANOVA, respectively. Differences between medians were assessed using the Wilcoxon-Mann-Whitney rank-sum test, or the Kruskall-Wallis test. $P < 0.05$ was considered statistically significant and is given as "P", if all three groups were compared in one test, or "P1 vs. 3", if only group 1 was compared to group 3, respectively.

Ethical considerations

The Swiss IBD Cohort Study (SIBDCS) has been approved by the Ethics Committee of the Canton of Zurich (EK-1316). All patients signed the informed consent and the current sub-study has been evaluated and approved by the scientific board of the SIBDCS.

Results

Study population

Out of 3326 SIBDCS patients screened between 2006 and 2018, 408 patients were included in the final analysis, with 234 having CD, 154 having UC and 20 having IBDU (*Figure 2*). Patient characteristics are shown in *Tables 1*, *2* and *3*. Based on the defined distance groups, median patient proximity to specialist was 3.6 km (group 1, IQR 1.9 - 5.8 km), 20.8 km (group 2, IQR 15.4 - 27.6 km) and 45.8 km (group 3, IQR 40.5 - 49.2 km). Group 1 (62%) contained more male patients than group 2 (48%) or group 3 (51%) (P = 0.03). Median disease duration was longer in group 1 (6 years), than in group 2 and 3 (both 4 years) (P < 0.01). Median age at diagnosis was lowest in group 2 (21 years) than in group 1 (28 years) and 3 (26 years) (P < 0.01). There were no differences in IBD-types between groups.

The detailed clinical characteristics of CD patients according to PTSD are listed in *Table 2*. Differences were found in the following characteristics: Patients in group 1 had a longer median disease duration (7 years, IQR 3-9 years), than patients in groups 2 and 3 (both 4 years, both P < 0.01). Median age at diagnosis was lowest in group 2 (19 years) than in group 1 (28 years) and 3 (27 years) (P < 0.01). Patients in group 3 had the shortest diagnostic delay (median 2 months, IQR: 2-14 months), while the diagnostic delay was longer in group 1 (5 months, IQR: 2-22 months) and group 2 (7 months, IQR: 3-14 months) (P1 vs. 3 = 0.05).

The disease behavior differed between groups (P = 0.01, P1 vs. 3 = 0.01): patients in group 1 had more often a stricturing behavior (B2 + B2p, 27.3%) than a non-stricturing-and-non-penetrating behavior (B1 + B1p, 58.6%) compared to group 2 (B2 + B2p, 12.4%; B1 + B1p, 77.8%) and 3 (B2 + B2p, 14.8%; B1 + B1p, 74.1%), respectively. Local complications (fistulas, stenoses, abscesses) were not different between groups.

Out of all extraintestinal complications triggered by CD only aphthous and oral ulcers occurred more often in patients of group 1 (P = 0.04, P1 vs. 3 = 0.03).

Detailed clinical characteristics of UC and IBDU patients according to PTSD are shown in *Table 3*. Differences were found in the following characteristics: Group 1 (72%) contained more male patients than group 2 (53%) or group 3 (45%) (P = 0.01). Median disease duration was longer in group 1 (5 years), than in group 2 (4 years) and group 3 (3 years) (P = 0.02). The disease location differed at diagnosis between groups (P < 0.01): patients in group 2 had more often left-sided colitis (43.1%), while group 3 had more often proctitis (31.6%). At the last follow-up, disease localization did no longer differ between groups.

Treatment of CD Patients

Detailed treatment information is summarized in Table 2. At the time of enrollment, patients in group 1 (25%) were treated more often with 5-aminosalicylates (5-ASA) than patients in group 2 (8%) and group 3 (11%) (P < 0.01). There was no difference for the use of anti-TNF agents, steroids, antibiotics, calcineurin inhibitors, immunomodulators and other biologicals between groups.

At the time of last follow-up, anti-TNF agents were used more often in group 1 (51.5%) than in group 2 (43.3%) and group 3 (33.3%, P = 0.09, P1 vs. 3 = 0.03). There was no difference for the use of 5-ASA, steroids, antibiotics, calcineurin inhibitors, immunomodulators and other biologicals between groups at follow-up.

Analyzing the drug treatment at any time during the entire study period, 71.7% of patients in group 1 were treated with anti-TNF agents compared to 61.7% in group 2 and 55.6% in group 3 (P1 vs. 3 = 0.04). In addition, during the entire study period CD patients of group 1 had a higher use of 5-ASA (44.4%) than patients of group 2 (29.6%)

and group 3 (27.8%) (P = 0.04). Intestinal resection, fistula and abscess surgery were not different between groups.

Treatment of UC/IBDU patients

Detailed treatment information is summarized in Table 3. At the time of enrollment, UC and IBDU patients in group 1 (40.6%) and in group 2 (38.9%) were more often treated with steroids than in group 3 (15.8%) (P = 0.02). Especially systemic steroids were used more often at enrollment in group 1 (34%) than in group 3 (16%) (P1 vs. 3 = 0.04). Of note, topical steroids were only used in group 1 at enrollment (*ref. Table 3*). At the last follow-up, group 1 (25%) still used more steroids than group 2 (20%) and group 3 (5%) (P = 0.03). Also topical steroids were used more often at follow-up in group 1 (12%) than in group 2 (2%) and group 3 (5%) (P = 0.01). Over the entire study period, the usage of topical (group 1: 26%, group 2: 13%, group 3: 5%, P = 0.01) and systemic steroids (group 1: 73%, group 2: 72%, group 3: 55%, P1 vs. 3 = 0.05) decreased with increasing distance from the tertiary referral centers. The application of 5-ASA, antibiotics, immunomodulators, anti-TNF agents or other biologicals as well as calcineurin inhibitors was not different between groups and did not change over time. The frequency of surgery was not different between groups.

Discussion

To optimize therapy of IBD, patients need access to specialized care and close monitoring of therapy and development of complications, as well as periodical endoscopies. Distance and travel time could negatively influence the implementation of these measures and affect the disease outcome.

In this multicenter cohort study of Swiss IBD patients, a shorter distance to an IBD specialist was related to an increased use of 5-ASA and anti-TNF agents in CD as well as an increased usage of particularly topical steroids in UC patients. In CD, diagnostic delay was shortest in patients living at a larger distance to the specialist. The incidence of a more severe disease course, as represented by the number of surgical interventions, was not related to a longer patient-to-specialist-distance (PTSD), neither in CD nor in UC/IBDU.

Many studies have shown that an early initiation of medical treatment results in a better outcome in IBD patients [5, 16, 17]. Due to unspecific or mild early symptoms, diagnosing IBD can be demanding. Minimizing the diagnostic delay is – besides early immunomodulator/biological therapy – an important parameter to avoid complications and surgery [16, 18, 19]. To the best of our knowledge, the influence of distance to center on the diagnostic delay has not yet been investigated. Vavricka *et. al* showed that patients from the Swiss IBD Cohort Study are diagnosed with a delay of 9 months in CD and 4 months in UC [20]. In our study, the diagnostic delay was even shorter than previously reported [20] and we have seen a surprisingly low diagnostic delay of only two months in CD patients living over 35 km away from a tertiary IBD center. This observation might indicate a decreasing diagnostic delay within the last years, or also be related to the different sample size out of the same SIBDCS database in this study (408 IBD patients) compared to the above-mentioned Swiss study (1591 IBD patients).

Early treatment with immunomodulators has proven to reduce the risk of intestinal surgery, perianal surgery and other complications [21]. Other studies suggest that therapies with anti-TNF antibodies even appear to influence fistula healing in CD in a positive manner [17, 22]. The timing of such therapy is of great importance [23]. Another Swiss study showed that treatment with anti-TNF agents started within the first two years after diagnosis reduces the risk of developing intestinal strictures in CD [21]. In our study, the use of anti-TNF and immunomodulators at enrollment did not differ between PTSD groups, which could explain the non-existing difference in occurrence of CD-related complications and perianal fistulizing disease.

Our results are in contrast to a single-center study from Massachusetts that investigated the influence of distance between IBD patients and the Massachusetts General Hospital in Boston on disease outcome [13]. They found an increased need for IBD-related surgery, biologicals and immunomodulators in patients living at the largest distance from the specialist. Differences between the two studies might be related to different distances to the specialist. Our largest mean distance to specialist was 48.7 km, while it was 81.8 km in Massachusetts. It might be possible that our largest distance was not large enough to detect a difference in treatment and outcome. This is also supported ~~from~~by a study investigating the relationship between distance and outcome after cardiac operations [24]. The outcome was significantly worse in patients living beyond 100 km from the hospital – which is a much larger distance than analyzed in our study.

On the other hand, it has been demonstrated that biological therapy is more often prescribed at specialized centers [25]. From our database, we were not able to extract,

if patients were treated at a private practice or in an outpatient setting at the tertiary center. When the cohort study was initiated, it first began recruiting patients at the centers, and later in the periphery. It therefore might be possible, that patients living closest to the specialist were actually treated at a center, while the patients living at larger distances were treated at private practices. This might explain our finding that more patients living closest to the specialist were treated with anti-TNF agents (over 70% in group 1 were treated with anti-TNF agents~~))~~, if analyzing the medication received during the entire study period. This might also apply to our finding that more systemic steroids were used in patients living closest to the specialist in UC/IBDU. Corticosteroids are usually used when therapy with 5-aminosalicylates is insufficient [26, 27] or for treatment of an acute moderate to severe flare [27, 28]. Since we did not detect differences in disease outcome, it is likely that treatment differences between distance groups can be explained by the setting (private practice vs center) in which patients were treated. Telemedicine approaches might be an option to improve treatment outcomes for patients living at longer distances to the specialist.

Increasing disease duration in CD is – besides the above-mentioned delay in immunomodulator/biological therapy and increased diagnostic delay – a risk factor for repetitive CD-related intestinal surgery and complications [16]. We found a higher median disease duration in patients living closest to the specialist. The cumulative probability for intestinal surgery 10 years after diagnosis is 38% in CD and 25% in UC, respectively [8, 29]. In addition, previous studies found that specialized gastroenterologist in-hospital care results in lower in-hospital mortality risk [6, 30, 31], and in earlier surgical treatment [25]. However, although we expected a worse disease outcome with increasing PTSD, we did not detect a difference in the occurrence of surgical interventions between groups.

Our study bears several limitations. We excluded the majority of patients from the analysis, as they were enrolled into the cohort later than 6 months after the first presentation to a gastroenterologist. In contrast to the study from Boston [13], which was monocentric, we had to find a way to ensure stable distances, i.e. a stable address, between patients and IBD center from our cohort data, as address data might not have been constantly updated in the database. Compared to the study from Boston, we also had a lower difference between the distance groups: Groups 1 and 3 differed by 25 km. Given the fact, that the IBD centers were 70 to 100 km apart, we had to choose the distance groups accordingly. However, the rather small difference between the groups might have hampered the identification of more distinct differences. In addition, in the statistical analysis, we were not able to adjust for confounding factors, such as treatment duration (i.e., time on therapy, or if a therapy had to be stopped because of intolerance), socioeconomic status or insurance type, as this was not recorded in the database. These factors might have influenced treatment decisions.

Conclusion

In conclusion, our study shows that although differences in treatment with patient-distance-to-specialist exist, this does not seem to influence the diagnostic delay and disease outcome. This might be related to the small area, and therefore over-all short distances in Switzerland.

Conflict of Interest

The authors disclose no conflicts.

Author Contributions

MS and AS conceived and designed the project. MS supervised the project. MS and GR obtained funding. LG and SB analyzed the data and wrote the manuscript. NF and JBR performed statistical analyses. SRV, LB, JZ discussed the results and reviewed the manuscript. All authors approved the final version of the manuscript.

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Tables

Figure Legends

Figure 1. Map of Switzerland with place of residence of the study population and specialized health care facilities. Radius in kilometers: 0-10 km yellow, 10-35 km blue and > 35 km orange.

Figure 2. Flow diagram for inclusion criteria